High LET radiation can enhance TGFβ induced EMT and cross-talk with ATM pathways

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The TGFβ pathway has been shown to regulate or directly interact with the ATM pathway in the response to radiation in mammary epithelial cells. We investigated possible interactions between the TGFβ and ATM pathways following simulated space radiation using hTERT immortalized human esophageal epithelial cells (EPC-hTERT), mink lung epithelial cells (Mv1lu), and several human fibroblast cell lines. TGFβ is a key modulator of the Epithelial–Mesenchymal Transition (EMT), important in cancer progression and metastasis. The implication of EMT by radiation also has several lines of developing evidence, however is poorly understood. The identification of TGFβ induced EMT can be shown in changes to morphology, related gene over expression or down regulation, which can be detected by RT-PCR, and immunostaining and western blotting. In this study, we have observed morphologic and molecular alternations consistent with EMT after Mv1lu cells were treated with TGFβ. High LET radiation enhanced TGFβ mediated EMT with a dose as low as 0.1Gy. In order to consider the TGFβ interaction with ATM we used a potent ATM inhibitor Ku55933 and investigated gene expression changes and Smad signaling kinetics. Ku559933 was observed to reverse TGFβ induced EMT, while this was not observed in dual treated cells (radiation+TGFβ). In EPC-hTERT cells, TGFβ alone was not able to induce EMT after 3 days of application. A combined treatment with high LET, however, significantly caused the alteration of EMT markers. To study the function of p53 in the process of EMT, we knocked down P53 through RNA interference. Morphology changes associated with EMT were observed in epithelial cells with silenced p53. Our study indicates: high LET radiation can enhance TGFβ induced EMT; while ATM is triggering the process of TGFβ–induced EMT, p53 might be an essential repressor for EMT phenotypes.